Mechanism and prevention strategy of a bidirectional relationship between heart failure and cancer (Review)

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Abstract. The relationship between cancer and heart failure has been extensively studied in the last decade. These studies have focused on describing heart injury caused by certain cancer treatments, including radiotherapy, chemotherapy and targeted therapy. Previous studies have demonstrated a higher incidence of cancer in patients with heart failure. Heart failure enhances an over-activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, and subsequently promotes cancer development. Other studies have found that heart failure and cancer both have a common pathological origin, flanked by chronic inflammation in certain organs. The present review aims to summarize and describe the recent discoveries, suggested mechanisms and relationships between heart failure and cancer. The current review provides more ideas on clinical prevention strategies according to the pathological mechanism involved.

Contents

1. Introduction

Heart failure and cancer are two major diseases that affect human health, and they represent most causes of death and disability in humans (1,2), The incidence of heart failure and cancer in oldindividualshas increased quickly in the world (3,4). In previous studies, epidemiologists have revealed that cancer treatment makes patients more likely to suffer from heart failure; this cardio-oncology research focused on the prevention and treatment of cardiac damage caused by cancer treatment. Also, the cardiac damage caused by cancer treatment and treatment of cancer patients with heart disease are discussed in the present review (Table I) (3,5-12). A number of studies have suggested that patients with heart failure are more likely to have cancer (Table II) (13-25); however, the mechanisms and relationships between heart failure and cancer remain unclear. Certain studies have even confirmed the presence of a precancerous lesion before carcinogenesis in heart failure (26,27), and suggested that both heart failure and cancer are chronic low-level inflammatory diseases (26). The pathogenesis of heart failure caused by cancer treatment and the mechanism of cancer occurrence in patients with heart failure is currently unclear. The present review outlines the relationship between heart failure and cancer, and provides clinical strategies towards prevention according to the pathological mechanism.

2. Mechanism of heart failure in patients with cancer

Cancer has a high risk of associated cardiac toxicity, and treatments such as radiation, chemotherapy or immunosuppressive therapy can also severely affect the heart. At present, the mechanisms behind cardiac toxicity and treatment-associated effects are described in Fig. 1 and the following text (28,29).

Cardiotoxicity of chemotherapy and radiotherapy. Anthracyclines are commonly used as chemotherapeutic drugs for solid and hematological cancer types. Anthracyclines produce a large number of reactive oxygen free radicals, which consequently cause myocardial injuries (30). Anthracycline effects induce acute or chronic cardiotoxicity depending on the dosage of the drug, ranging from 5% (cumulative dose of 400 mg/m^2) to 26% (cumulative dose of 550 mg/m^2) cardiotoxicity (5,9). However, a study has reported that patients with hematological diseases treated with low doses of anthracyclines still have cardiac malfunction (31). This class of drug has the advantage that after its injection, it is intercalated into the DNA and blocks the activity of topoisomerase 2, which subsequently inhibits the proliferation of cancerous cells (32). It has been demonstrated that cardiac topoisomerase is a key mediator of doxorubicin-induced cardiotoxicity,

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which may reduce the efficacy of treatment (33,34). In fact, doxorubicin induces apoptosis and DNA damage in a topoisomerase-dependent manner; it also ultimately affects oxidative phosphorylation and mitochondrial biogenesis (34). Dexrazoxane, a topoisomerase inhibitor, is currently used as an effective drug for preventing and treating heart injury caused by radiotherapy and chemotherapy (35,36). Other studies previously revealed that angiotensin-converting enzyme inhibitors (ACEIs) prevented heart injury, and that, phosphoinositide 3-kinase γ removed damaged mitochondria in a heart failure model induced by Adriamycin, suggesting possible treatments to prevent anthracycline-induced cardiotoxicity (37,38). Radiotherapy is the most common treatment for breast cancer. Usually, patients who have received total radiation exposure of >30 Gy, with daily radiation exposure of >2 Gy, have radiation exposure to the left or front of the chest; without radiation protection, the heart can easily manifest symptoms of cardiac damage, including left main coronary disease and pericarditis (39,40). One study revealed that radiation therapy can directly cause myocardial damage through reactive oxygen species (ROS)-induced activation of Ca^{2+}/calmodulin-dependent protein kinase II (41). Radiation therapy can also cause vascular endothelial cell damage, which may contribute to coronary heart disease (6).

Targeted anticancer drug treatment causes heart failure. Trastuzumab, a monoclonal antibody against HER2, is an effective first-line drug for breast cancer (7). By binding to HER2, the trastuzumab molecule blocks the binding of human epidermal growth factor to HER2, thereby inhibiting the growth of cancerous cells (7). The cardiotoxicity of trastuzumab mostly results from symptomatic heart failure or subclinical left ventricular dysfunction (42). However, the effect of trastuzumab on the heart is reversible (43) through the activities of vascular endothelial growth factor (VEGF), which is an important regulator of angiogenesis (44). When cancer metastasizes, VEGF promotes neovascularization to provide nutrition to the cancer (44). The VEGF gene family consists of five members, which can activate downstream signaling pathways after binding to the corresponding VEGF receptor (VEGFR) (44,45); this phenomenon occurs by blocking the VEGF signaling pathway and includes the use of anti-VEGF/VEGFR monoclonal antibodies and VEGFR-tyrosine kinase inhibitor (TKIs). Drugs targeting VEGF signaling, including humanized anti-VEGF monoclonal antibody, humanized bevacizumab, TKIs and sorafenib, have certain cardiovascular side effects such as hypertension, thromboembolism and cardiomyopathy (44,46). It has been reported that the administration of bevacizumab combined with anthracyclines increases the incidence of heart failure from 4 to 14% (47). Meanwhile, VEGF can increase the release of nitric oxide, facilitate prostacyclin synthesis and decrease the expression of pro-inflammatory genes such as cyclooxygenase-2 and E-selectin. This suggests that anti-VEGF antibodies might cause hypertension and thromboembolic diseases (48,49). Certain studies have demonstrated that inhibitors of VEGF can damage endothelial cells and increase their microparticle production, while the microparticles can stimulate endothelial cells to generate certain reactions capable of causing further damage to the endothelial cells;

among those reactions, massive production of endothelin-1, excessive oxidative stress and inflammatory activation are the most commonly observed (46,50-52). In order to improve the safety of TKI drugs, the need for further studies and an improved understanding of the mechanism of cardiac injury appears crucial. Finally, cardiotoxicity is also related to proteasome inhibitors, which are useful for the treatment of multiple myeloma and other hematological malignancies. According to a meta-analysis, the second-generation proteasome inhibitor carfilzomib was associated with higher cardiotoxicity, with an 18% incidence of cardiovascular adverse events (53,54). Furthermore, in pigs, inhibition of the ubiquitin-proteasome system of cardiomyocytes led to decreased cardiac function and the generation of possible cardiac damage (55).

The human ether-à-go-go-related (HERG) gene belongs to the voltage-activated outwardly-rectifying EAG family of K^+ channels and is expressed in multiple tissue types, including cardiac, neural and smooth muscle tissues. HERG loss of function leads to long QT syndrome (56) and has been demonstrated to contribute to the occurrence of cancer. Furthermore, transfection of HERG can induce the malignant transformation of murine fibroblasts, while HERG blocker (dofetilide) can reverse this process (57). In previous, HERG channel antagonists have emerged as new target drugs for cancer treatment. However, the cardiotoxicity of HERG antagonists remains the major problem for this method of cancer treatment. HERG antagonists block the HERG channel, inhibit the proliferation and migration of cancerous cells, and inhibit the potassium channel of myocardial cells, resulting in severe arrhythmia (58,59). The most common arrhythmias are long QT syndrome and ventricular tachycardia; therefore, designing a drug that can be administered safely at a reasonable dosage is emerging as the main preventive strategy for HERG antagonist-related toxicity (60).

Cancer itself can cause heart failure. Cancer can cause cardiomyopathy, light chain amyloidosis and carcinoid heart disease. Amyloidosis is a disease that affects multiple organs, including the myocardium and heart valves in restrictive cardiomyopathy (61,62). Heart failure caused by light-chain amyloidosis is severe and might be related to the direct damage of light-chain amyloidosis in myocardial cells (8). Studies have also shown that oxidative stress may cause damage in myocardial cells (63,64). Currently, the treatment of events caused by cardiac light-chain amyloidosis is limited to the treatment of heart failure and related malignant cancer types, and there is no available treatment for light chain protein deposition (61). Carcinoid heart disease is caused by the release of vasoactive mediators, such as serotonin, bradykinin and histamine. Neuroendocrine tumors (NETs) are a rare type of cancer found in the gastrointestinal or respiratory tracts. Mediators released by NETs are inactivated in the liver and pulmonary blood vessels; therefore, carcinoid heart disease also occurs in the liver with cancer metastases in the stomach and intestines, which mainly damages the right ventricle, with bronchial carcinoids as an outcome (65,66). Carcinoid heart diseases are characterized by the formation of fibrotic plaques in the myocardium, which eventually leads to right-sided heart failure. In addition, fibrotic remodeling of the tricuspid valve results in regurgitation by the valve, leading

Table I. High risk of heart failure observed in different cancers and certain cancer treatments that can damage the heart.

First author, year	Cancer	Anticancer therapy/drugs	Target	Heart failure	(Refs.)
Armenian et al, 2016	Multiple myeloma, lung cancer, non-Hodgkin's lymphoma, breast cancer	A variety of anticancer therapies	A variety of anticancer therapies	Compared with healthy individuals, the incidence of heart failure in patients with cancer is higher	(3)
Swain et al, 2003	Breast cancer and lung cancer	Doxorubicin	Topoisomerase 2	Incidence rate: 26%	(5)
Saiki et al, 2017	Breast cancer	Radiation	Coronary artery endothelial cells	Incidence rate: 18%	(6)
Slamon et al, 2001	Breast cancer	Recombinant monoclonal antibody	Anti-HER2	Incidence rate: 27%	(7)
Quarta et al, 2014	Immunoglobulin amyloid light-chain disease	Different therapies	Cardiac amyloidosis	Ventricular wall thickening	(8)
van Nimwegen et al, 2015	Hodgkin's lymphoma	Anthracyclines	DNA	Incidence rate: 11%	(9)
Laufer-Perl et al, 2020	Breast cancer	Recombinant monoclonal antibody	Anti-HER2	Incidence rate: 5%	(10)
Tian et al, 2020	Soft-tissue sarcoma	Doxorubicin	Topoisomerase 2	Incidence rate: 4.17%	(11)
Degens et al, 2020	Non-small cell lung cancer	Radiation	Coronary artery endothelial cells	Incidence rate: 7.6%	(12)

to decompensation of the right ventricle. Medical treatment of carcinoid syndrome is limited to somatostatin analogs, but this treatment is not effective for the heart muscle itself or valvular disease (67). Clinically, although amyloidosis and carcinoid heart disease are the only forms of heart failure caused by cancer, it has been demonstrated in other studies that certain cancer types may affect cardiac function by releasing cardiac toxic cancer-related metabolites (68,69). In rats, this mutation stimulates the accumulation and release of D-2-hydroxyglutarate, which impairs Krebs cycle activity in the heart and inhibits contractile function (70).

3. Mechanism of cancer in patients with heart failure

In the last decade, epidemiology studies have reported a high incidence of cancer in patients with heart failure (71,72). However, these studies only indicate the relationship between cancer and heart failure; meanwhile, its related mechanism is still unclear. Possible mechanisms that interfere in such relationships (73) are shown in Fig. 1 and described in the following text.

Hypothesis from circulation factors. As an endocrine organ, during heart failure, the heart can secrete a number of circulating factors, including B-type natriuretic peptide, which can be used for the diagnosis/risk stratification and prognosis of heart failure (1,74). However, various cancer-generated circulating factors influence surrounding organs (75,76). In

heart failure combined with cancer, increased secretion of important factors, including tumor necrosis factor, interleukin (IL)-6, IL-1 and VEGF, occurs. Numerous studies have shown that heart failure stimulates cancer growth. For example, Meijers et al (27) demonstrated that heart failure enhanced cancer growth in adenomatous polyposis coli mice. Compared with that in sham-operated mice, the number and size of the tumors in mice with heart failure increased by three-fold. The occurrence and development of cancer is related to cardiac remodeling markers such as left ventricular ejection fraction (LVEF) and myocardial fibrosis. In order to further verify these findings, Meijers et al (27) established a hemodynamic injury-free model and found that heart failure accelerated cancer growth. This suggested that heart failure stimulating cancer growth is not related to the myocardial infarction model, while some circulating factors secreted by the heart itself during heart failure may stimulate cancer growth (27). Certain proteomics studies discovered that several circulating protein factors were secreted into the blood during the occurrence of heart failure (77,78); those protein factors might have various effects on colon tissue *in vitro*. Among them, α-1-antichymotrypsin (SerpinA3) promotes cancer growth by phosphorylating Akt and ribosomal protein s6 *in vitro* (27). A community cohort study with a total of 8,592 subjects showed that over a follow-up time of 12 years, 1,132 subjects (13.1%) were diagnosed with cancer, and among these, 132 (11.7%) were diagnosed with colorectal cancer (27). The N-terminal

Table II. Patients with heart failure have a high risk of developing cancer.

First author, year	Follow-up, years	Non-cardiovascular deaths attributable to cancer, %	(Refs.)
Kjekshus *et al*, 2007	2.7	19.9	(13)
Linde *et al*, 2008	1	16.7	(14)
Moss *et al*, 2009	4	31.1	(15)
Ruschitzka *et al*, 2013	1.6	21.7	(16)
McMurray *et al*, 2014	2.3	27.8	(17)
Doval *et al*, 1994	1.1	25.0	(18)
Bigger, 1997	2.7	37.1	(19)
Kadish *et al*, 2004	2.4	66.7	(20)
Granger *et al*, 2003	2.8	47.8	(21)
McMurray *et al*, 2003	3.4	38.6	(22)
Roy *et al*, 2008	3.1	38.6	(23)
Tavazzi *et al*, 2008	3.9	44.5	(24)
Velazquez *et al*, 2011	4.7	31.5	(25)

pro-B-type natriuretic peptide is an independent risk factor for colorectal cancer in patients with heart failure, and the risk of cancer increases with increasing concentration of the peptide (27,79). Together, these studies indicate that the secretion of certain biomarkers produced by the heart is not only a signal of myocardial injury, but also affects the growth of distant cancer, possibly through cardiac exocrine effects. In addition, Bertero *et al* (26) conducted a study focusing on underlying mechanisms such as inflammation and neurohormones, which provided some preliminary evidence that heart failure could result from the adaptation of the body's environment to the onset or development of cancer.

Neurohormone activation. Activation of the renin-angiotensin-aldosterone system (RAAS) is one of the central compensatory homeostatic responses in patients with heart failure. RAAS activation functions to maintain blood pressure and cardiac output; however, chronic activation of RAAS can have deleterious effects on the heart, kidneys and blood vessels (80). In addition to systemic RAAS, most organ systems such as that of the heart, blood vessels and kidneys, and even cancerous cells, have local RAAS. The RAAS has different functions, hormones and receptors depending on its locality (81); for example, increased expression of angiotensin II receptor type 1 (AT1R) in cancerous cells suggests strong cancer aggressiveness and a poor prognosis (82). The regulation of RAAS may also affect the tumor size, although the results are inconsistent: Specifically, the angiotensin II (AngII)/AT1R axis is hypothesized to enhance tumor growth, while the AngII/AT2R signal serves the opposite role (83,84). RAAS inhibitors such as ACEIs or angiotensin II receptor blockers (ARBs) represent the cornerstone of heart failure treatment (85).

Oxidative stress. The ROS family is the key element for oxidative stress in eukaryotic cells. The heart inputs and outputs a consistent amount of energy and mainly relies on oxidative phosphorylation of mitochondria. ROS serve an important role in heart failure and cancer (86,87); however, oxidative

phosphorylation of mitochondria also serves an important role in cancer development (88). Studies have found that dietary fiber supplementation has positive effects on heart oxidative stress responses (89,90). In addition, glycolysis increases the probability of heart failure and glucose oxidation leads to lactic acid production. Also, in response to rapid cancer growth, pyruvate dehydrogenase (PDH) and PDH kinase (PDK) play a major role in mitochondrial oxidative metabolism, which leads to increased glycolysis. PDH inhibits glucose oxidation and converts pyruvate to acetyl-CoA (91). PDK can phosphorylate and inhibit PDH. During heart failure, PDK is upregulated, but PDH is inhibited (91). Similar mechanisms for PDK upregulation and PDH inhibition are also present in cancerous cells (92). Dichloro-acetate, a PDK inhibitor, enhances PDH activity during heart failure, decreases ischemic damage and improves cardiac function; these changes consequently decrease the incidence/development of cancer (92).

Inflammation. Inflammation is closely related to heart failure. Heart failure increases inflammatory factor secretion, which supports the premise that inflammation leads to heart failure (93). Increased secretion of inflammatory factors during heart failure can cause bone marrow dysfunction. However, there is no direct evidence that proinflammatory cytokines released by cardiac cells affect cancer cells. Furthermore, Meijers *et al* (27) found that certain inflammatory factors, such as high-sensitivity C-reactive protein and central adrenomedullin precursors, are predictors or warning signs of cancers. The IL-1 inhibitor canakinumab decreased major cardiovascular events by 25% [hazard ratio (HR), 0.75; 95% confidence interval (CI), 0.66-0.85] in patients with myocardial infarction (94). Canakinumab also significantly decreased the incidence and mortality rate of lung cancer [highest dose (300 mg): HR, 0.33; 95% CI, 0.18-0.59; P<0.0001; and HR, 0.23; 95% CI, 0.10-0.54; P=0.0002, respectively] (95).

Immune system. Immune system dysfunction is closely related to the occurrence and development of cancer and
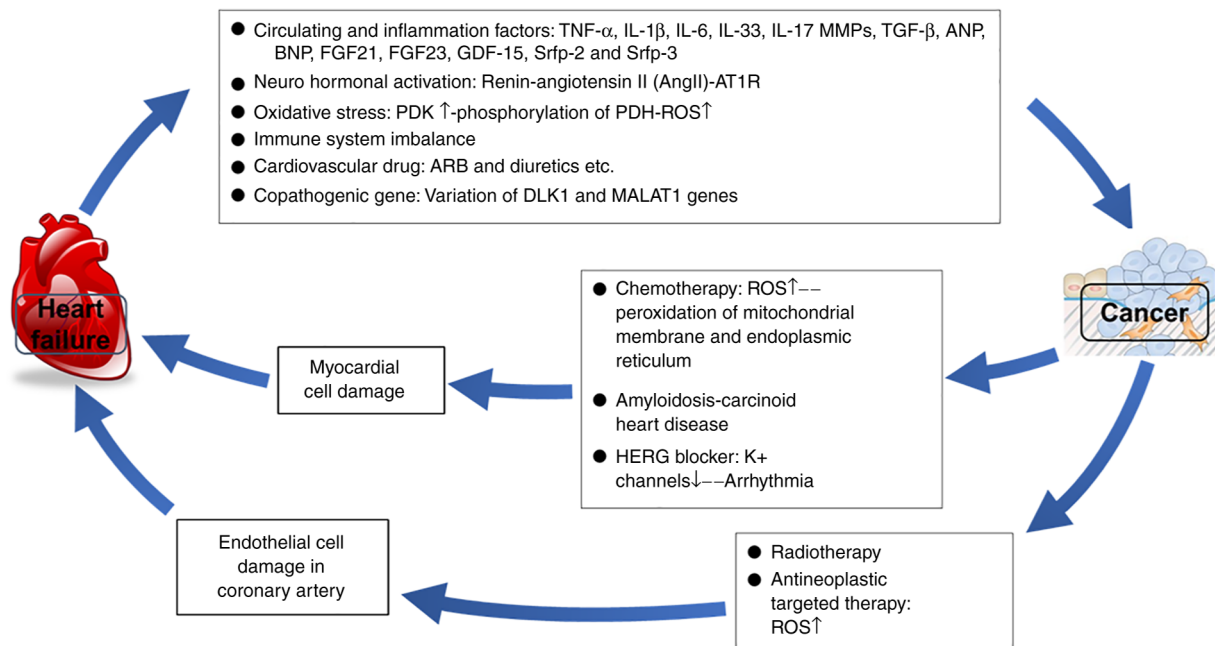
Figure 1. Mechanisms underlying the bidirectional relationship between heart failure and cancer. Myocardial and endothelial damage in coronary artery cause heart failure, which releases different inflammatory factors, activates RAAS and results in an imbalanced immune system. These pathophysiological changes lead to or promote cancer development. In turn, different treatments for cancer cause myocardial and endothelial damage in the coronary artery. AT1-R, angiotensin II receptor type 1; AngII, angiotensin II; PDH, pyruvate dehydrogenase; PDK, PDH kinase; ROS, reactive oxygen species; ARB, angiotensin II receptor blockers; DLK1, delta like non-canonical notch ligand 1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; HERG, human ether-à-go-go-related.

heart failure (96,97). In the early stage of body damage, a large number of immune cells are beneficial; such cells are able to decrease and repair the area damaged by injury, but chronic immune activation will generate severe side effects in the body, such as severe or even fatal allergic reactions (98). A complete overview of immune system dysfunction and heart failure has recently been published by the Working Group on Myocardial Function of the European Society of Cardiology (99). It is important to note that the pathogenesis of heart failure is particular. As well as the differing pathophysiological mechanisms of heart disease, the immune activation methods of heart disease also vary. For example, during the first stage of myocardial infarction (a few hours), neutrophils invade the heart and start the inflammatory response immediately; furthermore, the infiltration of macrophages breaks down necrotic tissue and promotes scar formation. In the next stage of remodeling, the inflammatory response is weakened; the secreted cytokines will regulate the invasion of inflammatory cells after myocardial infarction (100-102). Heart failure with a normal ejection fraction is mostly due to obesity, hypertension, diabetes and metabolic syndrome (103). Recent studies have revealed that the immune system may also play a certain role in heart failure with a normal ejection system, in this case, cardiac hypertrophy and fibrosis often occur. In heart failure with ejection fraction retention, macrophages are involved in the process of cardiomyocyte apoptosis and cardiomyocyte fibrosis, but a decrease in macrophages can reduce myocardial hypertrophy. Immune system dysfunction is related to the development of cancer, as cancers can spread to different organs by weakening the immune system (104).

Cardiovascular drugs may cause cancer. To date, the impact of cardiovascular drugs on cancer is still unclear. A number of meta-analyses on all types of antihypertensive drugs showed that the use of ARB, ACEIs, β-receptor blockers, diuretics and calcium channel blockers has relatively increased the incidence of cancer and the risk associated with cancer death by 5.0-10.0% (105,106). However, some meta-analyses have confirmed that antihypertensive drugs are not associated with carcinogenesis and development (107,108). Studies on patients with type 2 diabetes showed a negative correlation between losartan and cancer risk; however, overall, candesartan and telmisartan resulted in an increased rate of cancer incidence (109). Another drug that affects cancer is aspirin. A study has found that the use of a low dose of aspirin results in the acceleration of the progression of cancer in older individuals (≥70 years old), potentially because aspirin inhibits antitumor inflammatory or immune responses, which regulate later stage growth and metastasis (110).

Gene-related hypothesis. Myocardial fibrosis leads to cardiac remodeling, promoting heart failure. It has been indicated that the delta like non-canonical notch ligand 1 (DLK1) gene is a key factor during the differentiation of fibroblasts into myoblasts (111). The knockdown of the DLK1 gene leads to the downregulation of microRNA-370 (miR-370), activates the TGF-β/Smad3 pathway and promotes myocardial cell fibrosis (112). Excessive deposition of extracellular matrix infiltrated by myofibroblasts can cause cardiac dysfunction (112). However, DLK1 is a type of imprinted gene that participates in the regulation of the differentiation of a variety of cells; its expression is increased in a number of cancer types, such as liver,

pancreatic and colorectal cancer. Therefore, this gene plays an important role in carcinogenesis and cancer development (113). Sialyl-Lewis X (sLex) is the smallest recognition motif of the P-selectin ligand, which plays an important role in the adhesion and migration of cancerous cells. A study has found that miR-370 can specifically inhibit sLex expression and inhibit cell adhesion in colo-320 cells (114), justifying the fact that, inhibition of the DLK1 gene and downregulation of miR-370 lead to myocardial fibrosis/heart failure and cancer metastasis. Thus, some common targets might exist for heart failure and cancer. The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) gene has previously been shown to be involved in the proliferation, metastasis and function of cancerous cells and the reproduction of endothelial and smooth muscle cells (115,116). Studies have found that MALAT1 is the key regulatory factor of mouse atherosclerosis, where its knockout can significantly increase coronary plaques and affected area (117). Also, a decrease in MALAT1 expression in patients with coronary plaques is associated with a poor prognosis (including heart failure, arrhythmia and sudden death) (118). At present, there is no study to determine which genes are directly related to heart failure and cancer, thus identification and characterization of genes involved in both cancer and heart failure is required to improve cancer therapeutic methods in the future.

4. Prevention strategies

Strategies for preventing heart failure in patients with cancer. From the perspective of pathogenesis, the main cause of heart failure in patients with cancer appears to be cardiac toxicity caused by cancer-related treatment. At present, the protective measures for such injury mainly include two schemes: The use of cardioprotective agents and standardized rehabilitation exercise (Fig. 2). The cardioprotective agents mainly include the use of traditional drugs, such as ACEI, to inhibit myocardial remodeling and topoisomerase inhibitors. In a recent meta-analysis, 15 patients within randomized controlled trials were selected to analyze the protective effect of myocardial remodeling drugs on preventing cardiac toxicity induced by cancer treatment. The study found that aldosterone antagonists, ACEIs, statins and β-blockers could substantially improve left ventricular systolic function, while ARBs displayed no cardioprotective effect and failed to improve the left ventricular systolic function (measured as LVEF) (119). However, another study proposed that ARBs are effective in the prevention of heart failure. The study found that patients administered acetyl-based chemotherapy had a moderate yet significant benefit in terms of LVEF following use of β-blockers or ACEIs/ARBs. The β-blocker analysis included 769 patients with cancer, and the ACEI/ARB analysis included a total of 581 patients with cancer. The mean LVEF difference between ACEIs and ARBs groups was 4.71% (120). Topoisomerase is a new target to prevent cancer treatment-related cardiotoxicity, and dexamethasone and other topoisomerase inhibitors inhibit topoisomerase II (121). It has been reported that dapagliflozin protects against doxorubicin-induced cardiotoxicity in patients with breast cancer and diabetes. Moreover, dapagliflozin inhibits doxorubicin-induced myocardial fibrosis and greatly improves cardiac function by inhibiting the apoptosis of cardiomyocytes and the generation of ROS (122). Therefore, topoisomerase inhibitors and dapagliflozin can protect the heart
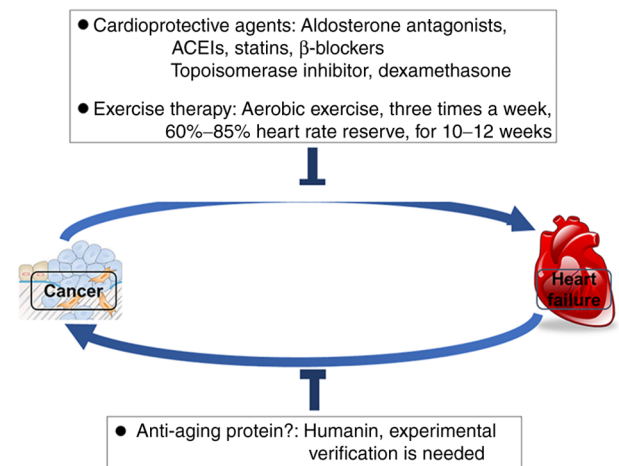

Figure 2. Prevention strategy for heart failure and tumors. Both cardioprotective agents and exercise therapy reduce heart failure and cancer development. The targeting of aging-related protein may be a strategy for heart failure and cancer in the future. ACEI, angiotensin-converting enzyme inhibitor.

from the toxicity of chemotherapy drugs by inhibiting myocardial remodeling.

Exercise therapy is a new treatment for cancer-related heart failure. Cardiorespiratory fitness (CRF) is closely related to the prognosis of patients with heart failure. CRF decreases with age, and short-term (12- to 26-week) anticancer therapy can reduce CRF by 26% (123). The maximum oxygen consumption rate represents the extent of CRF, which can be improved by exercise therapy in patients with cancer-related heart failure. MacVicar *et al* (124) formulated an intermittent aerobic exercise prescription for 45 patients with breast cancer who received different chemotherapy regimens. This treatment recommended exercise three times a week at 60-80% of the normal maximum heart rate, for 10 weeks. The VO$_2$ peak average of patients receiving this exercise prescription was increased by 40% compared with that of the non-exercise group. In another randomized controlled study, 20 patients with advanced breast cancer were randomly divided into two groups: The chemotherapy group and the chemotherapy + aerobic exercise group. After 12 weeks, the VO$_2$ peak of the chemotherapy group decreased by 9%, while the VO$_2$ peak of the chemotherapy + exercise group increased by 13% (125).

In addition to findings in breast cancer studies, another study found that exercise therapy was also effective for prostate cancer and Hodgkin's lymphoma, among others (126). Non-linear aerobic exercise could maintain the VO$_2$ peak in patients with prostate cancer, while it could increase the VO$_2$ peak in patients with Hodgkin's lymphoma from 5 to 17% (126). However, the impact of exercise therapy on the prognosis of cancer-related heart failure patients is controversial. In the follow-up period of 35 months, one study revealed that the all-cause mortality and readmission rate increased in the exercise group compared with that in the non-exercise group, and the VO$_2$ peak showed no significant difference between the two groups (127). However, this result needs to be further confirmed due to the lack of a long-term exercise therapy group as a control. Other studies have previously shown that exercise therapy can improve the VO$_2$ peak and the short-term prognosis in patients with

cancer-related heart failure (128,129). Therefore, non-linear aerobic exercise is the recommended exercise for patients with cancer-related heart failure. It was advised that the patients keep non-linear aerobic exercise three times a week for 10-12 weeks and the exercise intensity was 60-85% of the normal maximum heart rate (128,129).

Strategies for the prevention of cancer in patients with heart failure. There are currently no drugs or treatments that can prevent cancer in patients with heart failure. As the mechanism by which patients with heart failure are more likely to develop cancer is known, the inhibition of excessive inflammation during myocardial remodeling can be a good asset (Fig. 2). Both heart failure and cancer are aging-related diseases. Rochette *et al* (130) found that the anti-aging protein humanin (HN), which is a 24-amino acid, endogenous, mitochondrial-derived peptide, can inhibit myocardial remodeling and inflammation. Studies have found that HN can protect cardiomyocytes through anti-oxidative stress (131,132); furthermore, Qin *et al* (133) demonstrated that the exogenous injection of HN analogs could inhibit age-related myocardial fibrosis, while HN was able to inhibit cancer metastasis. In fact, it has been revealed that HN was able to inhibit the lung metastasis of mouse melanoma cancer cells (134). However, whether HN can prevent cancer in patients with chronic heart failure is currently debated. Large-scale clinical randomized controlled trials and animal studies are needed to prove its effectiveness in the future.

5. Conclusion

With the increase in anticancer drugs discoveries and prescriptions, the incidence of cancer-related heart disease has recently increased. Heart failure affects the development of cancer through a variety of mechanisms. Therefore, cancer and heart failure are related and interact with each other, by sharing some usual risks, such as hypertension, diabetes mellitus and obesity, and even pathogenic genes. The pathophysiological mechanism of heart failure and cancer remains to be explored in depth. Currently, preventive strategies are limited to heart failure in patients with cancer. Further clinical trials are required to determine how to prevent patients with heart failure from suffering from cancer.

Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

YZ conceived the study. HC and YZ wrote the manuscript. HM, PC, HC and YZ revised and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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